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Th 17 cells interplay with Foxp3$^+$ Tregs in regulation of inflammation and autoimmunity

Jietang Mai, Hong Wang, Xiao-Feng Yang

Department of Pharmacology and Cardiovascular Research Center, Temple University School of Medicine, Philadelphia, PA 19140

TABLE OF CONTENTS

1. ABSTRACT

T helper 17 cells (Th17) are a new CD4$^+$ T helper subset that has been implicated in inflammatory and autoimmune diseases. Th17, along with CD4$^+$CD25^{high} Foxp3$^+$ regulatory T cells (Tregs) and other new T helper subsets, have expanded the Th1-Th2 paradigm. Although this new eight-subset paradigm significantly improved our understanding on the differentiation and regulation of CD4$^+$ T helper subsets, many questions remain to be answered. Here we will briefly review the following issues: *a)* Old Th1-Th2 paradigm versus new multi-subset paradigm; *b)* Structural features of IL-17 family cytokines; *c)* Th17 cells; *d)* Effects of IL-17 on various cell types and tissues; *e)* IL-17 receptor and signaling pathways; *f)* Th17-mediated inflammations; and *g)* Protective mechanisms of IL-17 in infections. Lastly, we will examine the interactions of Th17 and Treg in autoimmune diseases and inflammation: Th17 cells interplay with Tregs. Regulation of autoimmunity and inflammation lies in the interplays of the different T helper subsets, therefore, better understanding of these subsets' interactions would greatly improve our approaches in developing therapy to combat inflammatory and autoimmune diseases.

2. INTRODUCTION

Interleukin-17 is a pro-inflammatory cytokine derived mainly from T cells, and also from neutrophils, monocytes, macrophages, mast cells, and vascular smooth muscle cells (1-5). IL-17 has been implicated in modulating various inflammatory and autoimmune diseases in human and mouse models, including tissue transplant rejection (6), asthma (7), scleritis, uveitis (8), rheumatoid arthritis (9, 10), systemic lupus erythematosus, encephalomyelitis (11), colitis (12, 13), and diabetes (14, 15). Among cytokines and more specifically, pro-inflammatory cytokines, one of the reasons that IL-17 has attracted special attention is that a subgroup of $CD4^+$ T helper cells (Th cells) producing IL-17 has been characterized as Th17 cells. Very importantly, the emerging new multi-subset paradigm with six subsets of T helper cells, including type 1 T helper cells (Th1), type 2 T helper cells (Th2), follicular T helper cells (Tfh) (16, 17), Th9 (IL-9 producing) (18-20), Th17, and $CD4^+CD25^{high}Foxp3^+$ (Forkhead box P3 transcription factor) regulatory T cells (Tregs) (21, 22), has replaced the 20 year-old Th1-Th2 paradigm (23). This new paradigm has significantly improved our understanding on the differentiation of functional $CD4^+$ T helper cell subsets and T cell regulation of inflammation and autoimmunity. Of note, inducible Tregs and Th17 arise in a mutually exclusive fashion, depending on whether their differentiation programs are activated in the presence of TGF-beta (transforming growth factor-beta) or TGF-beta plus pro-inflammatory cytokines such as IL-6 (24). Despite the remarkable progress made, the interplays between pro-inflammatory IL-17/Th17 and anti-inflammatory Tregs in orchestrating various types of inflammation and autoimmune diseases remain to be elucidated. In this review, we will focus on the discussion of the current understanding and progress in this front.

3. OLD Th1-Th2 PARADIGM VERSUS NEW MULTI-SUBSET PARADIGM

3.1. The Th1-Th2 paradigm's crisis

The Th1-Th2 cell paradigm, which has been used to explain how hosts initiate different T cell responses to eradicate the invasion of various pathogens, was first proposed 20 years ago by Mosmann and Coffman (23). Th1 cells are associated with cell surface expression of chemokine receptors CCR5 (Chemokine C-C motif receptor 5) and CXCR3 (CXC-chemokine receptor 3), and Th2 cells with CCR3 and CCR4 (25-27). Th1 associated cell surface molecules include CD26 and lymphocyte activation gene-3 whereas Th2 associated surface molecules include CD62L, T1/ST2, and CD30 (28). The signature cytokines for Th1 and Th2 are interferon-gamma (IFN-gamma) and IL-4, respectively. Th1 cells also secrete IL-2, tumor necrosis factor-alpha (TNF-alpha), and lymphotoxin (LT), which are important in mediating delayed type hypersensitivity reactions and macrophage activation. Th2 cells also secrete IL-5, IL-9, IL-10, and IL-13. Th1 cells are important in cellular immunity against virus and intracellular pathogens. Th2 cells are critical in humoral immunity, aid in B cell proliferation, and are important in allergic responses and protection against infection of helminthic parasites (23, 29). This paradigm has been the cornerstone to our understanding of T cell responses until recent years. However, it is apparent that there are many complicated pathological conditions that cannot be simply clarified by the Th1-Th2 paradigm. For a long time, autoimmune diseases are thought to be mainly driven by the auto-reactivity of Th1 cells as shown in T cell passive transfer studies. For example, Th1 cells were thought to have a pathogenic function in the development of experimental autoimmune encephalomyelitis (EAE), which suggested that IFN-gamma producing Th1 cells have specificity for self-antigen and are pathogenically required for the induction of organ-specific autoimmunity in EAE. However, the depletion of IFN-gamma gave contradictory results. IFN-gamma-deficient and IFN-gamma receptor-deficient mice and mice lacking other factors involved in Th1 lineage differentiation develop more severe disease rather than being protected from the disease (30, 31). Another example of how Th1-Th2 paradigm fails to address autoimmunity is seen in the relationship between IL-12 and IL-23. IL-12 is a cytokine important in Th1 differentiation. IL-12 and IL-23, each made of two subunits and these two cytokines share a common subunit, p40 and each have a unique subunit, p35 (IL-12) and p19 (IL-23) (32), respectively. It is shown that loss of IL-23 renders animals highly resistant to the development of autoimmunity and inflammation whereas the lack of IL-12 did not. The loss of IL-12 suggests that Th1 cells are not required for the induction of autoimmune-mediated inflammation (33). Taken together, thus, Th1-Th2 paradigm could not completely explain these new results, which lead investigators to search for new subsets and propose a new multi-subset paradigm.

3.2. New $CD4^+$ Th subsets – Tregs, Th17, Th9, Tfh, IL-10 IFN-gamma-secreting $CD4^+$ T cells and $CD4^+CD28^{null}$ T cells

Since 1990, several new $CD4^+$ Th subsets have been characterized:

3.2.1. Tregs

Tregs have an important role in suppressing both innate and adaptive immune responses (34-36). The naturally occurring Tregs have a major role in modulating the activity of self-reactive cells. The identification of Foxp3 as the critical determinant for Tregs development and function has generated expanded interest in studying the balance between autoimmunity and regulatory mechanisms in human autoimmune diseases.

3.2.2. Th17

Th17 is a distinctive subset of $CD4^+$RORgamma $t^+IL23R^+CCR6^+CD161^+$ IL-17-producing T cells (37-39), which is different from Th1, Th2, Tfh (16), Th9 (18-20), and Treg cell subsets. Th17 cells and their effector cytokines are involved in the pathogenesis of various autoimmune diseases and in mediating host defensive mechanisms against various infections such as extracellular bacterial infections.

3.2.3. Th9

In the presence of TGF-beta and IL-4, IL-9 producing cells are distinct from Th1, Th17, and $Foxp3^+$ Tregs. Th9 does not express any well-characterized

transcription factors, such as T-box expressed in Th1 cells (T-bet), trans-acting Th2-cell-specific transcription factor GATA3, Th17-specific retinoid-related orphan receptor gamma t (RORgamma t), and Tregs-specific Foxp3. Th9 cells are neither anergic nor suppressive, and Th9 cells vigorously proliferate and enhance T cell proliferation. These results suggest that Th9 cells represent a new subset of T helper cells. The specific transcription factor uniquely expressed by Th9 cells remains to be identified (18-20).

3.2.4. Tfh

After the requirement of T cell association for B cell production of antibody was observed in the 1960s, it took more than 30 years before the follicular $CD4^+$ T cell subset was characterized. Tfh cells have a unique ability to home to the B cell follicles in germinal centers owing to their expression of CXC-chemokine receptor 5 (CXCR5) and subsequently to induce antibody production (16, 17). Of note, Th1, Th2, Th9, Th17, and Tregs are localized in the T cell zone and circulation, whereas Tfh cells are the only $CD4^+$ T helper cells localized in the B cell follicles (17). New evidences suggest some aspects of the relationship between Th subsets: *a)* Tfh can be generated from Tregs, which challenges the current view that Tfh and Tregs are different subsets (40); *b)* Tfh can produce IL-17 without expressing Th17-specific transcription factor RORgamma t (41, 42); and *c)* inducible Tregs and Th17 cells arise in a mutually exclusive manner (24).

3.2.5. IL-10 IFN-gamma-secreting $CD4^+$ T cells

A new $CD4^+$ T cell subset, IL-10 IFN-gamma-secreting $CD4^+$ T cells were first reported in the early 1990s. They are suppressive T cells, which are able to inhibit cytotoxic T lymphocytes. These $Foxp3^-T\text{-}bet^+$ cells have a similar function but are distinct from conventional Tregs. IL-10 IFN-gamma-secreting $CD4^+$ T cells are activated in chronic infection and are responsible for prolonged infection. However, the relationships between IL-10 IFN-gamma-secreting $CD4^+$ T cells and other $CD4^+$ T cell subsets remain unclear (43).

3.2.6. $CD4^+CD28^{null}$ T cells

It has been reported that $CD4^+CD28^{null}$ T cells are an unusual subset of helper T cells, which expand and have deleterious effects in atherosclerosis and coronary artery disease. However, it is unclear whether $CD4^+CD28^{null}$ T cells have overlaps with Th1 and Th17 subsets (44).

4. STRUCTURAL FEATURES OF IL-17 FAMILY CYTOKINES

IL-17 was originally cloned from an activated T cell hybridoma using subtractive hybridization method in rodents. Initially, it was named cytotoxic T-lymphocytes-associated antigen 8 (CTLA-8). This protein was shown to have 57% homology with the 13^{th} ORF of a T-lymphotropic virus, herpes virus Saimiri virus (initially HVS13, later vIL-17) (45), the significance of which was not completely understood. The human IL-17 cytokine cDNA was cloned from a $CD4^+$ T cell library and it was found to have 63% amino acid homology to mouse IL-17. IL-17 (also IL-17A) is the founding member of the IL-17 cytokine family, which consists of six cytokines designated IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. IL-17 consists of 155 amino acids and is secreted as a disulfide-linked homodimeric glycoprotein (46). Of the six related cytokines identified in the family, IL-17 and IL-17F have the greatest homology, approximately 55%; IL-17F is also secreted as a disulfide-linked dimer (47, 48). IL-17B and IL-17C have approximately 28% amino acid homology with IL-17 (49). IL-17E has about 20% homology with IL-17, IL-17B, and IL-17C (50). IL-17F, like IL-17, is produced by T cells, whereas other members are produced by non-T cell tissues (47, 49, 50). Using techniques such as immunoprecipitation followed by immunoblot, enzyme-linked immunosorbent assay (ELISA), and mass spectrometry, IL-17 and IL-17F are found to exist either as homodimers or heterodimers with each other *in vitro* and in activated human $CD4^+$ T cells. All three forms of IL-17 and IL-17F are also found to have biological activities. IL-17F is found to be expressed at the highest concentration followed by IL17A/F heterodimer whereas IL-17 homodimer detection is minimal in activated T cells from human donor (51). In mouse, IL-17A/F heterodimer has also been detected, which has an important role in neutrophil recruitment in the airways and activation of fibroblast and macrophages to produce other pro-inflammatory cytokines (52, 53). The 3-dimensional crystalline structure of IL-17F reveals that IL-17 family members form a canonical pseudo-cystine knot (47). Several important questions remain unclear: (*a)* how the expressions of these IL-17 family members are regulated; and (*b)* how these IL-17 family members and other cytokines functionally interact in the regulation of inflammation and autoimmunity.

5. Th17 CELLS

The first member of IL-17 cytokine family was characterized over 15 years ago. But only recently, the cells that uniquely produced these cytokines were characterized. In addition to $CD4^+$ T cells, IL-17 and IL-17F were found to be produced by a number of other cell types such as gammadelta T Cells, natural killer T cells (NKT), neutrophils, eosinophils, monocytes (54, 55), and vascular smooth muscle cells (4). However, these two cytokines are mainly secreted by active $CD4^+$ T cells (48, 56, 57). Studies in IL-17 and IL-17F lead to the classification of a unique $CD4^+$ T cell subset named T helper 17 (58, 59). Besides IL-17 and IL-17F, Th17 cells also secrete other cytokines such as IL-21, IL-22, IL-26, and CCL20 (60-62).

As discussed above, Th17 is a distinctive subset of $CD4^+$ T cells, which is different from Th1, Th2, Tfh (16), Th9 (18-20), and Treg cell subsets. Th17 cells and their effector cytokines are involved in the pathogenesis of various autoimmune diseases and in mediating host defensive mechanisms against various infections, such as extracellular bacterial infections. Differentiation of naïve $CD4^+$ T cells into effector T helper cells requires initiation by their T-cell receptor and co-stimulatory molecules. Th17 is unique from the other lineages in that it requires

co-stimulatory molecules distinct from those required by other T cell lineages (33, 61, 63-68), and that Th17 is implicated in immune responses different from those of Th1, Th2, and Tregs. Th1 cells require IL-12 for development and they produce primarily IFN-gamma, IL-2, and LT to orchestrate T cell-mediated immunity (69). Th2 cells develop in the presence of IL-4, and the differentiated Th2 cells in turn produce IL-4, IL-5, and IL-13 to facilitate the humoral immune response (70). It has been found that cytokines and transcription factors unique to other subsets have the ability to inhibit the development of Th17 cells. For example, IFN-gamma produced by Th1, and IL-4, product of Th2 cells, negatively regulate Th17 development and IL-17 expression. Th17 cell differentiation is inhibited by transcriptional factors specific for Th1 and Th2 cells, STAT1 (Signal Transducer and Activator of Transcription), STAT4 and T-bet, STAT6 and GATA3, respectively (57, 58). Furthermore, Th17 promoting cytokines also suppress the development of other T cell lineages (64). This finding suggests that the balance of the T cell lineage is regulated by the products of each subset, and that during an infection, the proper T helper cell activation is crucial for the host to sufficiently combat and control the infection. However, in some studies, it has been observed that a subset of Th17 cells can co-produce IFN-gamma and IL-17, suggesting that IFN-gamma may not always inhibit IL-17 production, but rather plays a role in the pathogenic functions of Th17 (37, 71, 72). The function of IFN-gamma in Th17-mediated pathogenesis remains to be investigated.

In recent years, the cytokines and transcription factors involved in the generation, differentiation, and expansion of Th17 have been examined. However, there are still controversies to the exact conditions for Th17 development, especially in humans. TGF-beta, IL-6, IL-21, IL-23, and IL-1beta are the factors that have been found to be involved in Th17 differentiation and development in humans and rodents with some variance among the species. RORgamma t, RORalpha , STAT3, interferon-regulatory factor-4 (IRF4) (73), and the activator protein (AP)-1 B cell-activating transcription factor (Batf) are the five transcription factors identified in promoting the differentiation of Th17 from naïve T cells (1, 74). RORgamma t is a transcriptional factor specific for Th17 cell development, and the up-regulation of RORgamma t is dependent on STAT3 (75-77).

TGF-beta, produced by a variety of cells, is a critical cytokine in the development, homeostasis, and tolerance of T cells. TGF-beta is found to be an essential differentiation factor in the development of Tregs. Tregs inhibit inflammation and autoimmunity by counteracting the effects of other T helper cells. TGF-beta, produced by $Foxp3^+$ (as we recently reviewed (78)) Tregs, inhibits Th1 cell differentiation (79). Numerous reports have shown that TGF-beta is crucial in Th17 development in mice and humans (65, 80, 81). However, others report that TGF-beta may not be necessary for Th17 lineage commitment in humans, but a common consensus regarding which factors drives Th17 cells development in humans remains elusive (82-84). In mice, TGF-beta and IL-6 are important in driving the development of Th17 in naïve T cells while IL-21 and IL-23 are critical in maintaining and expanding Th17 (61, 64). *In vitro* study has shown that TGF-beta stimulation of T cells drives the development of Tregs (85), but the addition of pro-inflammatory cytokines such as IL-6 to T cells in the presence of TGF-beta favors Th17 differentiation (Figure 1). Also, the effect of IL-6 and TGF-beta to induce Th17 cells is amplified when IL-1beta and TNF-alpha are used as co-stimulators (63, 67). TGF-beta is required for the induction of IL-17 and IL-23 receptor (IL-23R) in naïve T cells, which make Th17 responsive to IL-23. IL-23 is another cytokine important in Th17 cell differentiation (86). IL-23 stabilizes the expansion of Th17 cells, and the IL-23R is induced in T cells after stimulation with IL-6 plus TGF-beta (65). However, high concentration of TGF-beta has been shown to inhibit the expression of IL-23R on T cells, suggesting that TGF-beta has a biphasic function in T cell development (1). At the transcriptional level, TGF-beta up-regulates RORgamma t expression on T cells, but it inhibits the expression of IL-17 in naïve T cells and drives Treg differentiation. Only with the addition of pro-inflammatory cytokines such as IL-6 is this inhibition mitigated (87). IL-6 induces the expression of IL-21, which in turn induces IL-23R expression as observed. The induction of IL-23R is nearly abolished in the absence of IL-21R. Since IL-21 is produced by Th17 cells, IL-21 can induce Th17 cells (66) and IL-17 production via positive feedback. IL-21 is found to suppress TGF-beta-induced expression of Foxp3 during Treg differentiation (60). IL-6, IL-21, and IL-23 all have the ability to independently induce RORgamma t expression, which is dependent on STAT3. In T cells lacking STAT3, IL-17 induction is completely lost in the presence of IL-6 or IL-21 with TGF-beta (68). However, they are not sufficient to induce Th17 differentiation alone. Th17 expression is only seen when TGF-beta is also present, suggesting that RORgamma t alone is not enough to induce Th17 differentiation either. Additional factors induced by TGF-beta are required to drive Th17 proliferation. Thus taken together, IL-6, IL-21, and IL-23 act in conjunction with TGF-beta to induce RORgamma t-dependent differentiation of Th17 cells. STAT3 is also found to be activated downstream of IL-6, IL-21, and IL-23. STAT3 and RORgamma t act together to induce maximal IL-17 differentiation. In addition, the small molecule halofuginone (HF) selectively inhibits mouse and human Th17 cell differentiation by activating a cytoprotective signaling pathway, the amino acid starvation response (88). Moreover, IL-1 receptor I $(IL\text{-}1RI)^+$ memory Th17 cells have increased gene expression of IL17, RORC (RAR-related orphan receptor C), and IRF4 even before T-cell antigen receptor triggering, indicating that the effect of IL-1beta is programmed in these cells via IL-1RI. Although Th17 cells from human umbilical cord blood did not express IL-1RI, the cytokines IL-7, IL-15, and TGF-beta up-regulated IL-1RI expression on naïve Th17 cells, suggesting that $IL\text{-}1RI^+$ naïve Th17 cells develop in the periphery (89).

6. EFFECTS OF IL-17 ON VARIOUS CELL TYPES AND TISSUES

IL-17 cytokines have numerous effects on a wide array of cell types in terms of inducing chemokines and cytokines production. The cytokine profile varies from cell

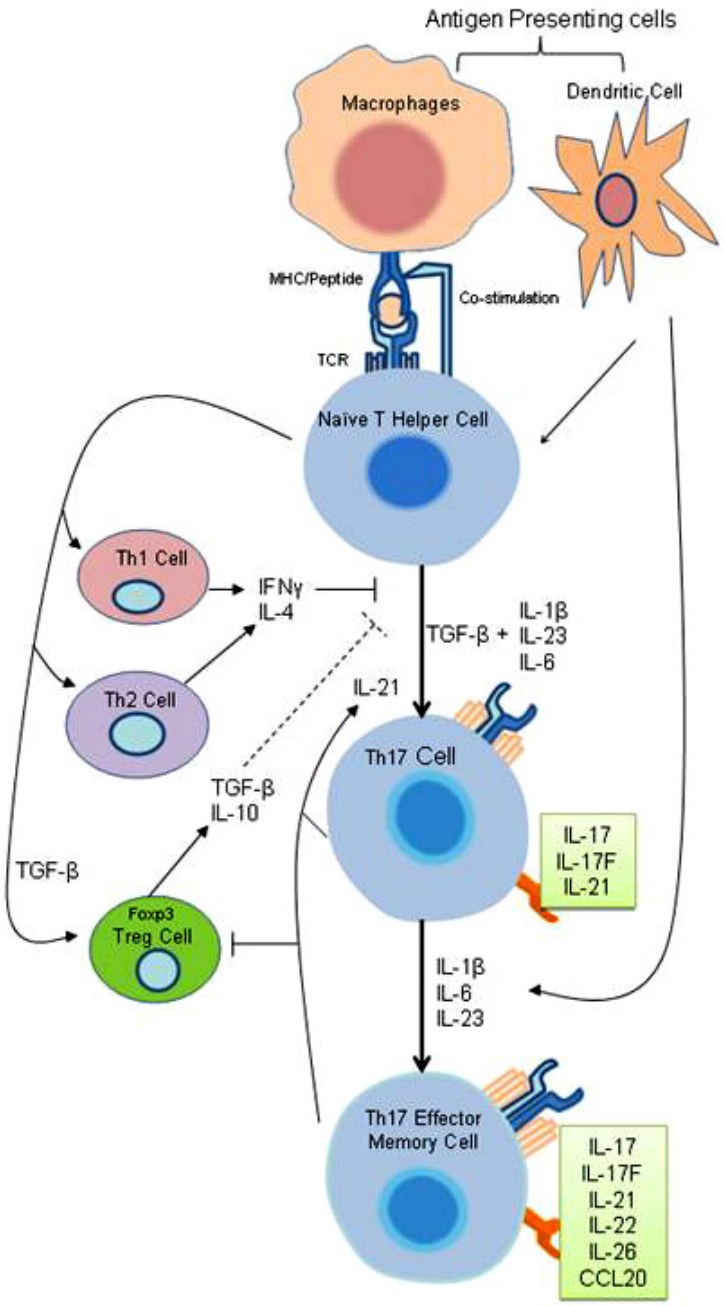

Figure 1. Th17 Cell Differentiation. Upon activation by antigen presenting cells, naïve T helper cells can differentiate into different T helper subsets. In the presence of TGF-beta and pro-inflammatory cytokines such as IL-6, IL-23, or IL-1beta, naïve T cell differentiates into Th17 cells. The differentiation of Th17 is inhibited by hallmark cytokines of other T helper subsets. Pro-inflammatory cytokines can induce further effector molecules in committed Th17 cells to establish their terminally differentiated effector phenotype.

types and the IL-17 cytokine(s) involved. Here we will discuss some examples.

6.1. Synovial stromal cells

Initially, the study of IL-17 shows that it induces IL-6 and IL-8 production in a dose-dependent manner in human foreskin fibroblasts. The incubation with IL-17 increases the surface expression of intracellular adhesion molecule-1 (ICAM-1) (46). In primary culture of synovial fluid, a similar effect is observed. IL-17 induces secretion of IL-6, IL-8, prostaglandin E2 (PGE2), and granulocyte colony-stimulating factor (G-CSF) by stromal cells which leads to the hematopoiesis of neutrophils. The recruitment

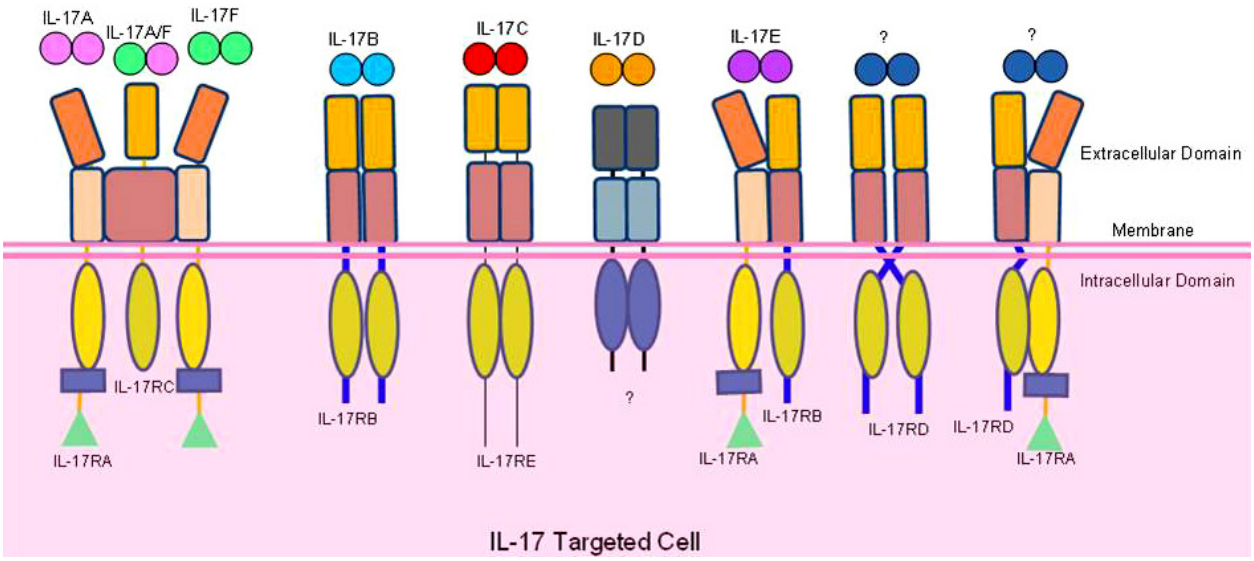

Figure 2. IL-17 Cytokine-Receptor Relationships. The IL-17 cytokine family has six members, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F. The IL-17 receptor family is made of five distinct receptors, IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE. The IL-17 receptor complexes through which IL-17 cytokines induce signaling are shown. The exact stoichiometry of each IL-17 receptor complex has not been completely elucidated. Ligands for the IL-17RD or IL-17RA-IL-17RD complex are yet to be identified. The receptor through which IL-17D induces signaling needs to be verified.

of neutrophils by IL-6 and IL-8 allows for the immune response to fight off infections (90).

6.2. Fibroblasts

IL-17F stimulates the production of cytokines such as IL-6 and IL-8 and G-CSF, and it has a role in cartilage matrix turn over via induction of matrix metalloproteinases (MMPs) (47). In fibroblastoid L929 cell line, IL-17 induces the mRNA expressions of monocyte chemotactic protein-1 (MCP-1), macrophage-inflammatory protein-2 (MIP-2), and tissue inhibitor of metalloproteinases (TIMP). In mouse embryonic fibroblast (MEF), granulocyte chemotatic protein-2 (GCP-2), MMP-3, MMP-9, and MMP-13 mRNAs are induced with IL-17 stimulation (91). In conjunction to several chemokines and cytokines, IL-17 also induces the production of various matrix metalloproteinases such as MMP-1, MMP-3, MMP-9, MMP-13, and TIMP-1 in fibroblasts, which are important in tissue remodeling in diseases such as inflammatory bowel disease, rheumatoid arthritis, and myocardial infarction (92-96).

6.3. Endothelial cells

IL -17F has a negative effect on angiogenesis in human endothelial cells and it induces endothelial cells to produce TGF-beta, IL-2, MCP-1, and lymphotoxin-beta (48). In contrast, IL-17 is shown to promote angiogenesis and tumor growth as seen *in vitro* with human umbilical venous cord endothelial cell (HUVECs), human dermal microvascular endothelial cell (HMVECs), tumor cell lines, and mouse fibroblasts. IL-17 promotes angiogenesis by up-regulating the production of various proangiogenic factors in fibroblasts and tumor cells including vascular endothelial growth factor (VEGF), PGE1, PGE2, keratinocyte-derived cytokines, and MIP-2 (97). In human endothelial cell culture, IL-17 is found to enhance the effects of various growth factors, such as basic fibroblast growth factor (bFGF), human growth factor (HGF), and VEGF, to induce proliferation of vascular endothelial cells (98). In addition, the expressions of IL-6, IL-10, IL-12, and PGE2 are also induced (99). IL-17 induces IL-6 production in endothelial cells, melanoma cells, MEF, splenic $CD11c^+$ cells, and $CD11b^+$ cells, and tumor cell growth in part via a STAT3 pathway (100). IL-25 (also known as IL-17E) is produced by brain capillary endothelial cells, and IL-25 protects against pro-inflammatory cytokine-induced excessive blood-brain barrier collapse through a protein kinase C epsilon-dependent pathway (101). Reversibly, endothelial cells also modulate Th17 differentiation. The C-type lectin-like receptors (CLECs) play crucial roles in immunity and homeostasis by recognizing pathogens as well as self-antigens. CLEC-1 is expressed at low levels by endothelial cells, which can be up-regulated by Treg cells and immunosuppressive cytokines IL-10 or TGF-beta, and down-regulated by inflammatory stimuli. CLEC-1 expression increases the differentiation of Th17 cells and decreases the differentiation of Tregs (102). In addition, VEGF induced by lipopolysaccharides (LPS) plays a key role in the activation of naïve T cells and subsequent polarization to Th1 and Th17 cells in the airway (103).

6.4. Vascular smooth muscle cells (VSMCs)

In cultured cells, IL-17 acts preferentially on VSMCs rather than endothelial cells to enhance production of pro-inflammatory mediators, including IL-6, and chemokines CXCL8 (IL-8) and CCL20 (6). IL-17 stimulates C-reactive protein expression in hepatocytes and VSMCs via p38 Mitogen Activated Protein Kinase (MAPK) and extracellular signal–regulated kinases 1 and 2

(ERK1/2)-dependent nuclear factor-kappaB (NF-kappaB) and CCAAT enhancer binding protein-beta (C/EBPbeta) activation (104). In addition, IL-17-induces the migration of VSMCs in a MMP-9-dependent manner and induces MMP-9 expression via similar pathways (105).

6.5. Monocytic cells and macrophages

While the effects of IL-17 and IL-17F have been well studied, the characterization of the effects of other cytokines in the IL-17 family has been limited. However, IL-17B and IL-17C are found to induce the release of TNF-alpha and IL-1beta from THP-1 cells (human acute monocytic leukemia cell line), a monocytic cell line, in a time and dose-dependent manner, but IL-17 was ineffective in the same condition. The different biological effects among IL-17 family members suggest that they function through different receptor-linked signal pathways. It was shown that IL-17B and IL-17C do not bind to the IL-17 receptor extracellular domain (49). In addition, IL-17 stimulates the production and expression of pro-inflammatory cytokines IL-1beta and TNF-alpha by human macrophages, which is completely suppressed by IL-4 and IL-10 but is partially inhibited by IL-13 and TGF-beta (99).

6.6. Structural lung cells

IL-17 induces hyperresponsive IL-8 and IL-6 production to TNF-alpha in structural lung cells (106). IL-17 is a weak stimulus of IL-8 and IL-6 production, but markedly enhances IL-8 and IL-6 responses to other stimuli, such as TNF-alpha. This modulatory effect of IL-17 is associated with a reduced IL-8 and IL-6 mRNA degradation and is not associated with its effect on IL-8 and IL-6 gene transcription.

7. IL-17 RECEPTORS AND SIGNALING PATHWAYS

7.1. IL-17 receptor family

IL-17 receptors make up a family of unique cytokine receptors (Figure 2). This cytokine receptor family consists of five members including IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE (47). The original IL-17 receptor, IL-17RA (IL-17R), was first characterized as a type I transmembrane protein of 866 amino acids with three domains including a 293 amino acid extracellular domain, a transmembrane domain of 21 amino acids, and cytoplasmic tail of 525 amino acids long (107). The mRNA of IL-17RA is found to be expressed extensively in various tissues and cell types including kidneys, liver, lungs, spleen, fibroblast cells, epithelial cells, T lymphocytes, and bone marrow stromal cells (107, 108). Furthermore, in humans, the IL-17RA protein is detected in peripheral blood T lymphocytes and in vascular endothelial cells (109). IL-17RA and IL-17RC are the well studied members of the IL-17 receptor family. IL-17RA is known as the receptor for IL-17A and IL-17RC for IL-17F (110). Although IL-17RA binds preferentially to IL-17A, it also has affinity for IL-17F (107, 111). IL-17RC also has been shown to have affinity for IL-17A in humans, whereas in mouse IL-17RC is specific only for IL-17F (110). Using fluorescence resonance energy transfer (FRET) microscopy, IL-17RA is shown to form pre-assembled complexes in the plasma membrane (112). Although each cytokine preferentially binds to one receptor over another, the biological activities of IL-17, IL-17F, and IL-17A/F require both receptors, IL-17RA and IL-17RC. The IL-17 receptors may exist as heterodimers or trimers forming an IL-17RA/RC functional receptor complex or other combinations of complexes although the exact stoichiometry is still unknown (113-115).

7.2. IL-17 receptor complex components

The extracellular domain of IL-17RA contains two fibronectin III-like (FN) domains (Figure 3). FN domain is a common feature of type 1 cytokine receptors and it is important in mediating protein-protein interaction and ligand binding (116, 117). IL-17RA and IL-17RC are members of the “similar expression to fibroblast growth factor genes, IL-17 receptors and Toll-like receptors-IL-1R” (SEFIR) protein family defined by their cytoplasmic SEFIR domain, which share homology with the TLRs/IL-R (TIR) domain. This structural homology suggests that IL-17R may share signaling pathways with Toll/IL-1 receptor. Indeed, activations of Toll/IL-1 receptor and IL-17 receptor pathways result in NF-kappaB activation and induction of inflammatory cytokines (118), but the signaling pathways upstream of each receptor are different. The SEFIR domain in IL-17R does not have the TIR box3 subdomain and the BB-loop, the structural elements found in the prototypical TIR domains (116). The IL-17RA does have a sequence homologous to the BB-loops at the carboxy-terminal side of the SEFIR domain, which is named TIR-like loop (TILL). The TILL domain is unique to the IL-17RA, whose functions and interactions in IL-17R signaling remain to be examined (119, 120). Another molecule found to be unique in IL-17R signaling is ACT1 (NF-kappaB activator 1, also known as TRAF3 interacting protein 2). Like IL-17 receptors, ACT1 is also part of the SEFIR protein family. ACT1 contains a SEFIR domain in its C terminus (121, 122). ACT1 is also found to be a negative regulator of B cell survival via its interaction with TRAF (TNF Receptor Associated Factor) 3 and CD40 and B-cell activating factor (BAFF) signaling (123), but in IL-17 signaling pathway ACT1 is a positive component and indispensable for IL-17-mediated biological activities. Since IL-17 receptors and ACT1 both contain SEFIR domain, it is believed that the interaction of IL-17 receptor with ACT1 is mediated by SEFIR domain. In addition to ACT1, TRAF6 has importance in IL-17 signaling. Because ACT1 contains a TRAF6 binding motif, ACT1 can bind to TRAF6, TRAF3, and TGF-beta-activated Kinase 1 (TAK1), thus, TRAF family proteins are critical in NF-kappaB activation (122). IL-17A/F has a synergistic effect with TNF-alpha to increase CXCL1 expression in macrophages from mice. CXCL1 expression is impaired when TRAF6 is absent in knock-out model, indicating that the receptor for IL-17A/F uses TRAF6 for its signaling (52). In addition to TRAF6, TRAF3, and TAK1 are also involved in IL-17 signaling since the TRAF6 binding motif of ACT1 can bind to TRAF3 as well as TAK1 (122). TAK1 is also involved in Toll/IL-1R activation of NF-kappaB and c-Jun N-terminal kinase (JNK) (124), suggesting that TAK1 may play a role in IL-17-induced NF-kappaB and JNK activation. Additionally, a domain

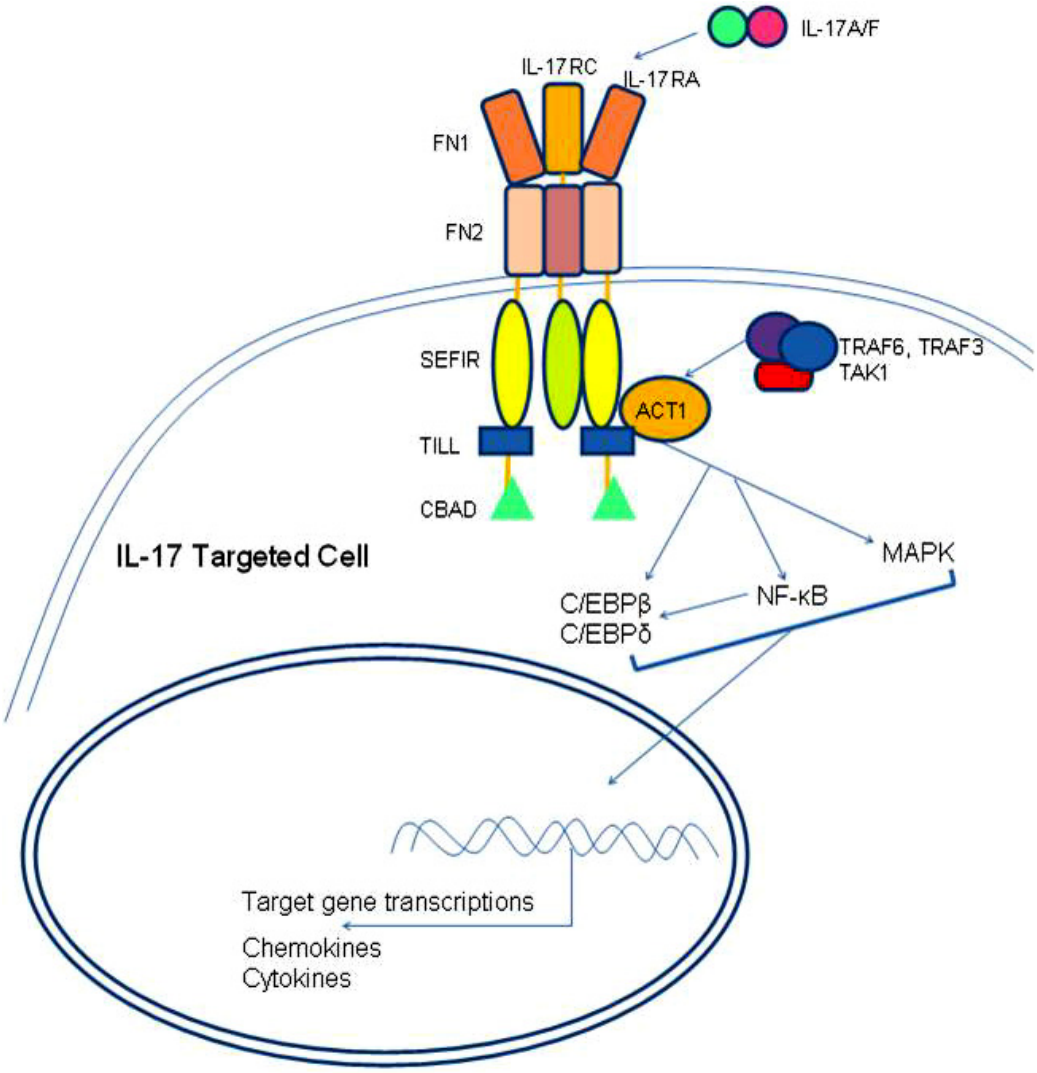

Figure 3. Main Structural Features of IL-17 Receptor and IL-17 Signaling Pathways. Extracellular domain of the IL-17 receptor has two fibronectin III-like domains (FN), which mediate ligand binding. Intracellular domain of IL-17 receptor contains a SEFIR domain, which defines IL-17 receptors as members of the "similar expression to fibroblast growth factor genes, IL-17 receptors and Toll-like receptors-IL-1R" (SEFIR) family. A TIR-like loop (TILL) and a C/EBPbeta-activation domain (CBAD) are found in IL-17RA intracellular domain. ACT1 is a critical adaptor protein in IL-17 signaling pathways. ACT1 associates with TRAF6, TRAF3 and TAK1 in mediating signals downstream of IL-17 receptor. IL-17 receptor pathways activates NF-kappaB, MAPK, C/EBPbeta and C/EBPdelta, which lead to target gene transcriptions of pro-inflammatory chemokines and cytokines.

called C/EBPbeta-activation domain (CBAD) has been identified in the C-terminal of IL-17RA. So far this domain is only seen in IL-17RA, which is required for IL-17A-mediated glycogen synthase kinase 3beta (GSK3beta) phosphorylation of C/EBPbeta (119, 120).

7.3. IL-17 receptor signaling

Although IL-17 cytokines have been shown to induce various cytokines and chemokines in numerous cell types via the interaction with their receptors, the detailed mechanism of the IL-17 signaling pathway remains unclear (Figure 3). Published studies show that IL-17 ultimately activates NF-kappaB and MAPK pathways in its signaling pathway to induce pro-inflammatory cytokines (94, 104, 125, 126). IL-17 has been shown, in gel shift analyses, to activate NF-kappaB via p50 and p65, which are the key components of the canonical NF-kappaB pathway (127). The involvement of IL-17 in the non-canonical NF-kappaB has not been defined, but NF-kappaB-inducing kinase (NIK) is a component of the non-canonical NF-kappaB that has shown to be induced in response to IL-17A (125). IL-17 is found to up-regulate the expression of CCAAT/enhancer binding proteins, C/EBP-delta and C/EBP-beta, which are important regulators in IL-6 transcription (127). Activation of MAPK pathway in IL-17 signaling is important in controlling the stability of mRNA

transcripts of pro-inflammatory cytokines via interactions with the AREs (AU-rich elements) of the 3' untranslated region of the transcripts (128). IL-17 activated MAPK pathway is shown to activate activator protein 1 (AP1) (129), but the exact mechanism by which IL-17 regulates mRNA stability needs to be clarified.

8. Th17-MEDIATED INFLAMMATIONS

8.1. Experimental autoimmune encephalomyelitis (EAE)/multiple sclerosis

Multiple sclerosis/EAE has pathological conditions which cannot be explained by the Th1-Th2 paradigm lead to the discovery of two other T helper cell subsets, Tregs and Th17. In the EAE models, the concept that Th17 cells are responsible for driving autoimmune inflammations is exemplified. EAE is induced by passive transfer of IL-17-producing memory activated T cells (61). Th1 cytokines, IL-12 and IFN-gamma, initially thought to induce EAE, instead suppresses IL-17 production, and are shown to have a protective mechanism in EAE. The disease is exacerbated when there is a lack of IL-17 suppression in IL-12 or IFN-gamma-deficient mouse models (61, 130, 131).

8.2. Inflammatory skin disease in mice and psoriasis in humans

Evidences suggest that Th17 cells, but not Th1 cells, play an important role in the pathogenesis of inflammatory skin disease: a) Higher frequencies of Th17 cells, IL-17A$^+$, IL-17A/TNF-alpha$^+$, and IL-17A/IFN-gamma$^+$ in psoriatic lesions but not Th1 cells; b) Anti-TNF-alpha therapy in psoriasis work by decreasing Th17 cells; and c) IL-15 triggers IL-17 from human T cell blasts and IL-15 gene variants (single nucleotide polymorphisms, SNPs) are associated with psoriasis (1).

8.3. Inflammatory bowel disease (IBD) (1)

Th17 cells are more potent in transferring IBD than Th1 cells (132). IL-17F increases dextran sulfate sodium (DSS)-induced colitis, while IL-17F knock-out mice are relatively protected. However, controversially, IL-17A is protective in DSS-induced colitis since IL-17A knock-out mice developed more severe disease (133). Anti-IL-17A monoclonal antibody treatment, presumably neutralizing IL-17A, aggravates DSS-induced colitis (13). Future work is warranted to solve this puzzle.

8.4. Experimental arthritis/rheumatoid arthritis (1)

IL-17 knock-out mice have reduced collagen-induced arthritis (134). Th17 cells through the secretion of IL-17A act on osteoblastic cells by inducing the expression of receptor activator for nuclear factor-kappaB ligand (RANKL). Interaction between RANKL on osteoclast precursors and RANKL results in the differentiation of osteoclasts and bone resorption (135). These results suggest that IL-17/Th17 cells play an important role in promoting the pathogenesis of arthritis. In patients with arthritis, higher concentration of IL-17 is found in the joints when compared to the controls. Up-regulations of MMP-1, -2, -3, -13 by IL-17 are seen in whole synovial tissue explant from rheumatoid arthritis patients, primary synovial fibroblasts, human cartilage, and chondrocyte cultures. Mild cartilage proteoglycan degradation is seen with IL-17 stimulation and the effect on proteoglycan is exacerbated with TNF-alpha or Oncostatin M co-stimulation (136).

8.5. Atherosclerosis

Th17 cells may also play an important role in modulating autoimmune responses in atherosclerosis (137-139). More broadly, in pathological states such as obesity, hypertension, diabetes, metabolic syndrome, and other cardiovascular disorders, perivascular tissue becomes dysfunctional. Production of protective factors diminishes while detrimental adipocytokines such as leptin, resistin, IL-6, TNF-alpha, or IL-17 increases (140). Induction of atherosclerosis by the Western-type diet in low density lipoprotein receptor deficient (LDLR-/-) mice with IL-17R-/- bone marrow transplantation (BMT) induces a 46% reduction in lesion size in the aortic root. The atherosclerotic plaque composition reveals no significant changes in collagen content and neutrophil counts, but a reduction in mast cell numbers and an increase in macrophage numbers. In addition, upon IL-17R-/- BMT the investigators observed a decrease in anti-oxLDL antibodies of the IgG class, a reduced IL-6 production, and an increased IL-10 production, suggesting that signaling via the IL-17 receptor in bone marrow derived cells enhances the process of atherosclerosis (141). Similar to that found in LDLR-/- mice, ApoE-/- mice, another atherosclerosis mouse model (36), reveal (*a)* significantly increased secretion of Th17 related cytokines, IL-17 and IL-6 and expression of RORgamma t; and (*b)* obviously decreased numbers in Treg cells, secretion of Treg related cytokine TGF-beta 1, and expression of Foxp3 as compared with age-matched wild-type C57BL/6J mice. Meanwhile, the expressions of Treg-related mediators are much lower in ApoE-/- mice than that in their age-matched wild-type littermates. These results suggest a potential role of Th17/Treg imbalance in the formation and progression of atherosclerosis (139). In supporting these findings, Li and colleagues showed that the IL-1 receptor associated kinase 1 deficient (IRAK-1-/-) mice have constitutively higher populations of Treg cells. In contrast, when stimulated with T cell antigen receptor (TCR) agonists together with IL-6 and TGF-beta , IRAK-1-/- CD4 Th cells exhibit attenuated STAT3 Ser727 phosphorylation and reduced expression of IL-17 and RORgamma t compared with that in wild-type cells. These results demonstrate that IRAK-1 deletion results in decreased IL-17 expression and dampened inflammatory responses in acute and chronic inflammatory mice including atherosclerosis (142). Controversially, Mallat and colleagues found that the loss of suppressor of cytokine signaling 3 (SOCS3) in T cells increases both IL-17 and IL-10 production, induces an anti-inflammatory macrophage phenotype, and leads to unexpected IL-17-dependent reduction in lesion development and vascular inflammation. *In vivo* administration of IL-17 reduces endothelial vascular cell adhesion molecule-1 expression and vascular T cell infiltration, and significantly limits atherosclerotic lesion development. These results identify novel SOCS3-controlled IL-17 regulatory pathways in atherosclerosis and

may have important implications for the understanding of the increased susceptibility to vascular inflammation in patients with dominant-negative STAT3 mutations and defective Th17 cell differentiation (138). However, the issue of how pro-inflammatory cytokine IL-17 plays a suppressive role in inflammatory autoimmune atherosclerosis in SOCS3-/- mice remains a mystery. Interestingly, adult SOCS3-null mice on a leukemia-inhibitory factor (LIF)-null background succumb to a spontaneous fatal inflammatory disease characterized by neutrophilia and inflammatory-cell tissue infiltrates, suggesting that genetic reduction of embryonic LIF production rescues placentation in SOCS3-/- embryos but does not prevent inflammatory disease (143, 144). Obviously, future work is needed to solve this controversy.

8.6. Diabetes

IL-17/Th17 cells play an important role in promoting diabetes. The dendritic cell (DC)-dependent loss in Tregs leads to an increase in the number of T cells producing inflammatory cytokines, such as IFN-gamma (Th1 cells) and IL-17 (Th17 cells). Loss of DCs leads to a loss of Tregs, and the remaining Tregs exhibit decreased Foxp3 expression. The increase in Tregs induced by DC expansion is sufficient to prevent type 1 autoimmune diabetes (145). Treatment with either neutralizing anti-IL-17 or recombinant IL-25 (IL-17E) has no effect on diabetes development in young (<5 weeks) non-obese diabetic (NOD) mice, a model of spontaneous autoimmune diabetes. However, either intervention prevents diabetes when treatment is started at 10 weeks of age ($P < 0.001$). Insulitis scoring and immunofluorescence staining reveal that both anti-IL-17 and IL-25 significantly reduce peri-islet T cell infiltrates and decrease GAD65 (Glutamate decarboxylase) autoantibody levels. In addition, Berberine, an alkaloid derivative from *Berberis vulgaris L.*, inhibits Th17 differentiation by activating ERK1/2 and inhibits Th1 differentiation by inhibiting MAPK and JNK activation. Berberine down-regulates the activity of STAT1 and STAT4 through the suppression of p38 MAPK and JNK activation. Berberine controls the stability of STAT4 through the ubiquitin-proteasome pathway and prevents the progression of type 1 diabetes in NOD mice (146). Similarly, innocuous IFN-gamma induced by adjuvant-free antigen suppresses diabetes and restores normoglycemia in NOD mice through inhibition of IL-17 production (147). In addition to the studies performed in mouse models of diabetes, the production of pro-inflammatory cytokines IL-17, TNF-alpha, and secretion of IL-6 by peripheral blood lymphocytes from patients with type 1 diabetes mellitus (T1D) is reduced, when the autoantigen-specific T cell clones are suppressed (148). Another study also suggests that there is a significant, although modest, increase in the frequency of IL-17-secreting cells in lymphocytes from long-term patients with T1D compared with healthy controls (149). These studies suggest that Th17 cells are involved in the pathogenesis of autoimmune diabetes and that IL-25 treatment results in a T-cell-mediated dominant protective effect against autoimmunity (14).

9. PROTECTIVE MECHANISMS OF IL-17 IN INFECTIONS

Th17 cells are powerful tissue inflammation inducers associated with various experimental and human autoimmune diseases. However, the extreme importance of Th17 cells appears to be in host defense especially in clearing of invaded pathogens, which are not sufficiently handled by Th1 or Th2 cells. IL-17 is found to be important in the defense against *Klebsiella pneumoniae* as seen in IL-23p19 knock-out (gene deficient, KO) mice and IL-17R KO models. IL-17KO mice are highly susceptible to infection of *K. pneumoniae* because IL-17 is important in the recruitment of neutrophils to the *K. pneumoniae* infection site (150, 151). In addition, IL-17 and IL-17F also induce anti-infection neutrophil infiltration into lung in the clearance of mycoplasma pneumonia in mouse models of acute respiratory tract infection (152). In another knock-out model, IL-17RA KO mice are more prone to *Candida albicans* infection in comparison to wild type mice. Also, when wild type mice are given IL-17 injection, they are protected from lethal doses of the pathogen (153). IL-17 or IL-17 in conjunction with IL-22 also up-regulates the expression of antimicrobial molecules such as beta-defensins in keratinocytes. Of note, defensins are antibiotics found in the skin, lungs, and gastrointestinal tract (53, 154). IL-17 also enhances the production of mucin in the airways, which traps pathogens in the lung mucosa (85).

10. Th17 CELLS INTERPLAY WITH Tregs

10.1. Updates of Tregs

The findings that the lack of Foxp3 expression, and consequently the absence of Tregs lead to both human and mouse autoimmune diseases have rapidly expanded knowledge of Tregs development and function during the past 5 years. In the previous sections, 3.2, 5, 8.5, 8.6, we have discussed some recent progress in characterizing Tregs. In the following section, we will highlight some additional progresses: (*1)* Human blood, isolated from an outbred population in a pathogenic environment, contains up to 30% $CD4^+CD25^+$ cells. Only the 2–4% of the cells with the highest CD25 expression can be considered regulatory. In addition to CD25, the best-accepted alternative is the lack of cell surface CD127 (IL-7 receptor). In addition, HLA-DR expression identifies a functionally distinct population of what appear to be terminally differentiated human Tregs (155); (*2)* Tregs recognize a wide range of antigenic specificities with increased reactivity to self antigens. The Treg repertoire is highly diverse with a distinct set of T-cell receptors (TCRs), and yet is overlapping to some extent with the repertoire of conventional T cells (156); (*3)* TGF-beta signaling is not required for thymic expression of Foxp3, nor is TGF-beta signaling or responsiveness required for *in vitro* suppressive activity of $Foxp3^+$ Tregs. TGF-beta treatment is capable of inducing both Foxp3 and RORgamma t expression, which leads exclusively to Treg differentiation. These data suggested that there is an alternative, extrathymic pathway for Treg differentiation (157); (*4)* $Foxp3^+CD4^+CD25^+$ Treg subsets that maintain

immunologic homeostasis have been considered to be a homogeneous population of naturally occurring, thymus-derived $CD4^+CD25^+$ T cells (nTregs). However, similar $Foxp3^+$ Tregs can be induced from $CD25^-$ precursors *in vivo*, and *ex vivo* with IL-2 and TGF-beta (adaptive Tregs, inducible Tregs, or iTregs). These two subsets differ in their principal antigen specificities and in the T-cell receptor signal strength and co-stimulatory requirements needed for their generation. Although IL-6 can convert nTregs to Th17 cells, iTregs induced by IL-2 and TGF-beta are resistant to this cytokine and thereby might retain suppressive function at inflammatory sites. Thus, nTregs and iTregs may have different roles in the adaptive immune response (158); (*5)* Tregs consist of lymphocytes with several phenotypic markers that share the ability to suppress, by various mechanisms, inflammatory responses. These Tregs consist of subsets such as IL-10 secreting type I Tregs and type III Tregs that produce TGF-beta, as well as iTregs and nTregs (159); (*6)* In autoimmunity, chronically activated Antigen Presenting Cells (APCs) under the influence of intracellular signaling pathways, such as phosphatidylinositol-3 kinase (PI3K), JAK-STAT, MAPK, and NF-kappaB pathways, can escape surveillance by Tregs, leading to the activation of T cells that are refractory to suppression by Tregs. Moreover, APCs and APC-derived inflammatory cytokines such as TNF-alpha, IL-6, IL-1beta, and IL-23 can render Tregs defective and can also reciprocally enhance the activity of the IL-17-producing pathogenic Th17 T cell subset. These results suggest that APC-Treg interactions play an important role in maintaining immune tolerance (160); (*7)* Treatment with nTregs resolves colitis (a $CD45RB^{high}CD4^+$ T cell transfer model of colitis), but only when iTregs are also present. Although iTregs require Foxp3 for suppressive activity and phenotypic stability, their gene expression profile is distinct from the established nTregs' "genetic signature," indicating that these two groups of Tregs have developmental and possibly mechanistic differences. These results have identified a functional role for iTregs *in vivo* and demonstrated that both iTregs and nTregs can act in concert to maintain tolerance (161, 162); (*8)* Epigenetics is defined by regulation of gene expression without altering nucleotide sequence in the genome. Several epigenetic markers, such as histone acetylation and methylation, and cytosine residue methylation in CpG dinucleotides, have been reported at the Foxp3 locus. In particular, CpG dinucleotides at the Foxp3 locus are methylated in naïve $CD4^+CD25^-$ T cells, activated $CD4^+$ T cells, and TGF-beta-induced iTregs, whereas they are completely demethylated in nTregs. The DNA methyltransferases DNMT1 and DNMT3b are associated with the Foxp3 locus in $CD4^+$ T cells. Methylation of CpG residues represses Foxp3 expression, whereas complete demethylation is required for stable Foxp3 expression (163); (*9)* The composition of the extracellular matrix provides contextual cues to leukocytes in inflamed and healing tissues. One example of this is hyaluronate (HA); Low molecular weight hyaluronate (LMW-HA) generated during active inflammation is a TLR ligand and an endogenous "danger signal," while high molecular weight-HA (HMW-HA) is predominantly in healing or intact tissues and functions in an inverse manner. HMW-HA actively promotes immune tolerance by augmenting Treg function, but LMW-HA does not. In a human iT (Reg) model, HMW-HA but not LMW-HA provides a co-stimulatory signal through cross-linking CD44, which promotes Foxp3 expression. Thus, HMW-HA contributes to the maintenance of immune homeostasis in uninjured tissue and effectively communicates an "all-clear" signal to down-regulate the adaptive immune system through Tregs after tissue matrix integrity has been restored (164); (*10)* Using *in vitro* functional assays and phenotypic analysis, Tregs isolated from patients with a variety of autoimmune diseases have been demonstrated to exhibit reduced regulatory function as compared with those isolated from healthy controls (165). Our laboratory among others has shown that loss of Treg function results in autoimmune responses (166, 167). We have characterized a Treg-specific, IL-2-dependent apoptotic pathway and demonstrated that Treg apoptotic/survival pathways are therapeutic targets for Treg-based immunotherapy (see our invited review) (21); and (*11)* Bluestone and colleagues recently reported that substantial percentages of cells have transient or unstable expression of the transcription factor Foxp3. These 'exFoxp3' T cells have an activated-memory T cell phenotype and produce pro-inflammatory cytokines. Moreover, exFoxp3 cell numbers are higher in inflamed tissues in autoimmune conditions. Adoptive transfer of autoreactive exFoxp3 cells leads to the rapid onset of diabetes. Finally, analysis of the T cell receptor repertoire suggests that exFoxp3 cells can be developed from both natural and adaptive Tregs. Thus, the generation of potentially autoreactive effector T cells as a consequence of Foxp3 instability has important implications for understanding autoimmune disease pathogenesis (168).

10.2. Reciprocally interconnected Th17 and Tregs

Regulatory T cells are the subset of T helper cells important in immune suppression and prevention of autoimmune diseases (169). It has been shown that IFN-gamma and IL-4, produced by Th1 and Th2 respectively, inhibit the differentiation of Th17. Tregs has been shown clearly to suppress Th1 and Th2 cell immune responses (170). However, the IL-17 production or Th17 cell development has not been shown to be down-regulated by Treg *in vitro* (37, 171) (see next section for the new results). The developmental programs of Th17 cells and adaptive Tregs are reciprocally interconnected (1, 172) (Figure 4). Upon TCR stimulation, a naïve T cell can be driven to express Foxp3 and become a Treg cell in the presence of TGF-beta. Immunosuppressive cytokine TGF-beta has a broad inhibitory effect on the immune system. TGF-beta alone induces Foxp3, which is the transcription factor required for Treg cell induction and maintenance. RORgamma t is the transcription factor crucial in Th17 development in naïve T cell. When T helper cells are differentiated into Tregs, RORgamma t expression is progressively extinguished and the opposite is seen in Th17 development when IL-6 is present (173, 174) (1). During an immune response, APCs such as dendritic cells in response to activation by microbial antigens produces IL-6. IL-6 acts in concert with TGF-beta to inhibit adaptive Treg generation and to induce Th17 cell differentiation (63, 65, 67). The balance of TGF-beta and IL-6 in adaptive Treg

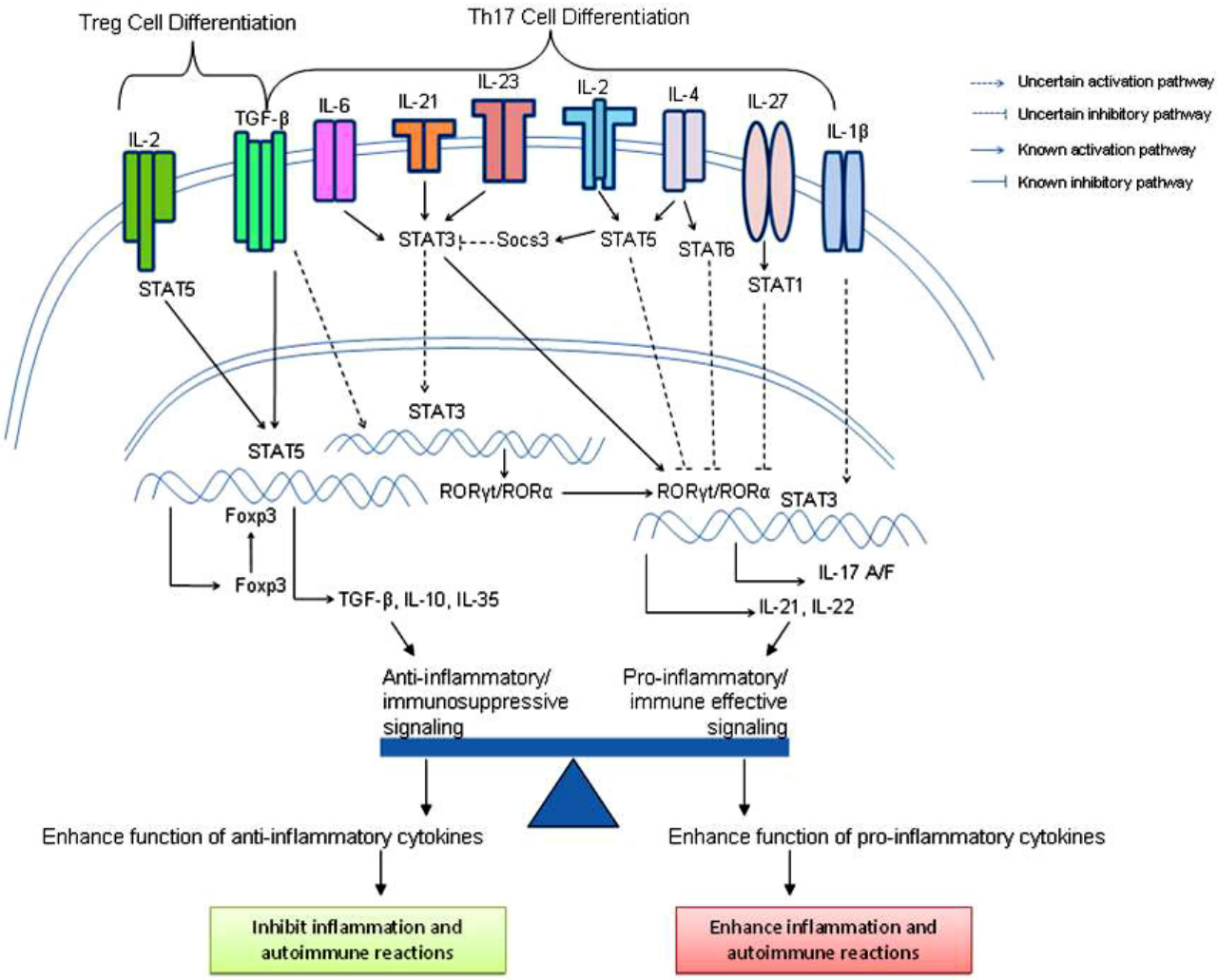

Figure 4. Interplay between Tregs and Th17 Lineages. Differentiation of $CD4^+$ T Cell is important for immune regulation and host defense. Signaling pathways in Tregs and Th17 differentiation show specific cytokines, receptors, and transcription factors involved in each lineage. TGF-beta is a common factor in the differentiation of two lineages with opposing effects. Effector cytokines of Tregs enhance anti-inflammatory/immunosuppressive effects and thus inhibit inflammation and autoimmune reactions. Effector cytokines of Th17 are pro-inflammatory and enhance inflammation and autoimmune reactions.

and Th17 differentiation shows the reciprocal relationship between adaptive Treg and Th17 cells. In the absence of inflammatory stimuli, TGF-beta-induced Tregs keep the immune system in balance by suppressing autoimmunity. In the presence of inflammatory assault, adaptive Treg generation is suppressed and Th17-induced pro-inflammatory responses are activated. In IL-6 KO (knock out) mouse model, the generation of Th17 is defective while there is an increase in the numbers of adaptive Treg generated (63, 64). Thus, IL-6 and IL-21 act as switch factors via controlling the Foxp3/RORgamma t balance (174). Both Th17-specific transcription factors RORgamma t and RORalpha physically interact with Treg-specific transcription factor Foxp3 to antagonize each other's functions (174) (175). The results from IL-6-/- deficient mice show a severe defect in the generation of Th17 cells and increased numbers of Tregs in peripheral T cell repertoire (60, 63). Additionally, IL-2, which is a growth factor to promote Treg generation and survival, inhibits Th17 generation. IL-2 receptor signaling promotes the generation of Tregs, but inhibits the production of Th17 cells in the periphery (176) (177). IL-2 deficient mice have decreased the numbers of Tregs while enhanced Th17 cell generation (176). These common gamma-chain cytokines, IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, activate STAT5, and the absence of STAT5 abrogates Treg differentiation. Both STAT5 deficient and IL-2 deficient mice have elevated serum levels of IL-17. The action of STAT5 works through binding the Foxp3 gene and inhibiting Th17 differentiation (178).

10.3. Inhibition of Th17 by Tregs

Evidence to date has indicated that Th17 cells are resistant to suppression by human $Foxp3^+$ Tregs. It has been recently demonstrated that CD39, an ectonucleotidase which hydrolyzes ATP, is expressed on a subset of human

natural Tregs. Although both $CD4^+CD25^{high}CD39^+$ and $CD4^+CD25^{high}CD39^-$ T cells suppress proliferation and IFN-gamma production by responder T cells, only the $CD4^+CD25^{high}CD39^+$, which are predominantly $Foxp3^+$, suppress IL-17 production, whereas $CD4^+CD25^{high}CD39^-$ T cells produce IL-17. These findings suggest that $CD4^+CD25^{high}Foxp3^+CD39^+$ Tregs play an important role in constraining pathogenic Th17 cells in patients with autoimmune inflammation (179).

11. CONCLUSIONS

The identification of Th17 $CD4^+$ T helper subset and Tregs as well as Th9 cells and Tfh cells significantly add to the old Th1-Th2 paradigm and substantially improve our understanding of the roles of T helper cell subsets in the processes of innate and adaptive immunity. Although much progress has been made in the characterization of Th17 cells and Tregs, the interactions of these two T helper subsets in various inflammatory and autoimmune disease models need to be further defined. Future works to better characterize the Th17 and Treg interplay in inflammation and autoimmune diseases (180) would eventually lead to the development of therapeutics for diseases such as atherosclerosis, diabetes, and arthritis.

12. ACKNOWLEDGEMENTS

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Send correspondence to: Xiao-Feng Yang, MD, PhD, FAHA, Department of Pharmacology, Temple University School of Medicine, 3420 North Broad Street, MRB 325, Philadelphia, PA 19140, U.S.A, Tel: 215-707-5985, Fax: 215-707-7068, E-mail: xfyang@temple.edu

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